REMARKS

Claims 1-25 are pending in this application. The examiner has rejected claims 1-25 under 35 USC §112, second paragraph. The examiner has rejected claims 1-17 under 35 USC §103(a) as unpatentable over Goertz (US 4,801,460) and Ortega (US 4,837,032). Claims 17-25 have also been rejected under 35 USC §103(a) as unpatentable over Noda (US 5,389,380) and Goertz in combination.

1. Response to rejection under 35 USC §112, second paragraph

The examiner argues that claims 1-25 are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. However, the claims have been amended to conform with the formal requirements of 35 USC §112, second paragraph. Accordingly applicants respectfully request the rejection be withdrawn.

2. Response to rejection under 35 USC §103(a) of claims 1-17

The examiner argues that one of ordinary skill in the art would have been motivated to prepare the instant composition in light of Goertz which discloses "a process of preparing sustained release theophylline composition where the process comprises heating a mixture of N-vinylpyrrolidone and vinyl acetate and theophylline at a temperature of 120° (examples 1 and 3)." Paper number 7, p. 7, 2nd paragraph. However, applicants' respectfully assert that Goertz does not teach a process comprising heating a mixture of N-vinylpyrrolidone and vinylacetate.

Goertz teaches a process of melt-extrusion of either a fusible NVP polymer (col.

1 line 55 to col 2, line 17) which is either a homopolymer obtained from N-vinylpyrrolidone as a monomer or a copolymer obtained by copolymerization of the monomers N-vinylpyrrolidone and vinylacetate. (Column 5, lines 3-10). The resulting copolymer forms a new polymer with essentially different properties from a mixture of two homopolymers. Goertz further discloses that the copolymer is admixed with an active ingredient, and the mixture is then processed by melt-extrusion, wherein the copolymer must be molten. (Column 2, lines 25-30).

Specifically, Goertz discloses:

> The polymeric binder must soften or melt in the total mixture of all components at from 50 to 180°C., preferably from 60°C to 130°C., so that the melt can be extruded.
>
> Column 2, lines 25-28.

In contrast, the instant invention utilizes polyvinylpyrrolidone grades with a molecular weight of 20,000 to 1,000,000. Utilization of polyvinylpyrrolidone at these molecular weights results in compositions with higher glass transition temperatures. Thus, the process of the instant invention, carried out at a maximum temperature of 130°C does not produce melt in the granulation. (Page 5, lines 10-15 of applicant's specification). For instance, polyvinylpyrrolidone with a molecular weight of 40,000 melts at 168°C. Support for this may be found in the attached affidavit of Dr. Karl Kolter describing the grass transition temperature of polyvinylpyrrolidone as a function of molecular weight. The data supplied therein clearly shows that as the molecular

weight of polyvinylpyrrolidone increases, the glass transition temperature also increases.

The process of the instant invention, carried out at a maximum temperature of 130°C does not produce melt in the granulation. For instance, polyvinylpyrrolidone with a molecular weight of 40,000 melts at 168°C. It is clear from this evidence that the polyvinylpyrrolidone does not melt during the granulation step of the instant process as polyvinylpyrrolidone of the molecular weights of claim 1 show a glass transition temperature above 130°C. Accordingly, the instant invention comprises a mixture of polyvinylpyrrolidone and vinyl acetate in contrast to the polymer as disclosed in Goertz.

Furthermore, the examiner argues that the instant invention is obvious in view of Ortega. However, Ortega discloses sustained release tablets formulated by wet granulating a mixture of theophylline and the acid insoluble polymer. (Column 4, lines 4-10). The instant process does not require the addition of a solvent or binder solution. Thus, Ortega discloses a very different process than that of the instant invention.

Together, the Goertz and Ortega references do not render the instant invention obvious. As discussed above the Goertz reference requires melting of the N-vinylpyrrolidone polymer in order to be extruded and Ortega requires a solvent suitable for a wet granulation process. Together, these references do not teach each and every element of the claimed invention. Namely, the references do not teach polyvinylpyrrolidone of a molecular between 20,000 to 1,000,000 wherein the formulated mixture of polyvinylacetate and polyvinylpyrrolidone acts both as binder and

a matrix former. Thus, these references do not suggest to one of ordinary skill in the art the mixture of the present invention and accordingly, the combination of the references fails to establish a *prima facie* case of obviousness.

3. Response to rejection under 35 USC §103(a) of claims 17-25

The examiner argues that claims 17-25 are obvious in view of 35 USC §103(a) in view of Goertz and Noda (US 5,389,380). Noda discloses a sustained release pharmaceutical preparation comprising a carrier, an effective ingredient layer and a coating layer. Thus, Noda teaches that a coating layer is necessary to achieve sustained release of the active ingredient. (Column 3, lines 35-40). Moreover, the coating layer requires a heat-meltable material as a binder. (Column 3, lines 50-55).

In contrast to the disclosure of Noda, the instant invention does not require melt in the granulation. Moreover, a *prima facie* case of obviousness has not been identified as, in the very least, there is no suggestion that it is possible to combine the active ingredient in the coating layer. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in combining a mixture of polyvinylpyrrolidone with the active ingredient, without melt, where the prior art teaches a covering layer to control the release of the pharmaceutical ingredient and requires polymeric melt.

Accordingly, the combination of Goertz and Noda does not render the instant invention obvious as both of the references would lead one to believe that a heat meltable material is required to provide sustained release of the pharmaceutical

preparation. Moreover, neither reference suggests that it is possible to utilize a non-meltable material to achieve the desired result. Thus, applicant's respectfully request the rejection be withdrawn as the references fail to establish a *prima facie* case of obviousness.

In view of the foregoing amendments and remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

Please find attached a check for $860.00 for the RCE and one month extension of time.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (currently amended) A process for producing an oral dosage form with sustained release of active ingredient, comprising

a) a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone

b) at least one active ingredient

c) optionally water-soluble polymers or low or high molecular weight lipophilic additives

d) and, optionally, ~~other~~ excipients,

wherein the mixture of a) to d) or a) to c) or a) and b) and d) or a) and b) is granulated by heating to from 40°C to 130°C, and

wherein the molecular weight of polyvinylpyrrolidone is between 20,000 and 1,000,000 and wherein the formulated mixture of polyvinylacetate and polyvinylpyrrolidone acts as binder and a matrix former.

3. (currently amended) A process as claimed in claim 1, wherein the active ingredient : water-soluble polymers or low or high molecular weight lipophilic additives ratio employed ~~in the combination~~ is from 5:95 to 85:15.

10. (currently amended) A process as claimed in claim 1, wherein production is possible ~~both~~ either continuously or batchwise.

11. (currently amended) A process as claimed in claim 1, wherein further processing of the granules, principally the forced screening, can take place ~~both~~ either in the hot state or in the cooled state.

17. (currently amended) An oral dosage form comprising

a) a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone

b) at least one active ingredient

c) optionally water-soluble polymers or low or high molecular weight lipophilic additives

d) and, optionally, ~~other~~ excipients,

wherein the mixture of a) to d) or a) to c) or a) and b) and d) or a) and b) is granulated by heating to from 40°C to 130°C.

24. (currently amended) The method of ~~using the oral dosage forms as claimed in claim 17 for producing drug products with delayed release of active ingredient~~ delaying the release of an active ingredient comprising producing the oral dosage forms of claim 17 as drug products.

25. (currently amended) The method of ~~using the oral dosage forms as claimed in claim 17 for the delayed release of active ingredients in the form of food supplements or additives, vitamins, minerals or trace elements~~ delaying the release of at least one active ingredient comprising producing the oral dosage form of claim 17 wherein the at least one active ingredient comprises food supplements or additives, vitamins, minerals or trace elements.

COMPLETE LISTING OF ALL CLAIMS IN THE APPLICATION

1. (currently amended) A process for producing an oral dosage form with sustained release of active ingredient, comprising

a) a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone

b) at least one active ingredient

c) optionally water-soluble polymers or low or high molecular weight lipophilic additives

d) and, optionally, excipients,

wherein the mixture of a) to d) or a) to c) or a) and b) and d) or a) and b) is granulated by heating to from 40°C to 130°C, and

wherein the molecular weight of polyvinylpyrrolidone is between 20,000 and 1,000,000 and wherein the formulated mixture of polyvinylacetate and polyvinylpyrrolidone acts as binder and a matrix former.

2. (previously amended) A process as claimed in claim 1, wherein the polyvinyl acetate to polyvinylpyrrolidone ratio is 6:4 to 9:1.

3. (currently amended) A process as claimed in claim 1, wherein the active ingredient : water-soluble polymers or low or high molecular weight lipophilic additives ratio employed is from 5:95 to 85:15.

4. (previously amended) A process as claimed in claim 1, wherein polyvinyl acetate and polyvinylpyrrolidone each have a molecular weight of from 20,000 to 1,000,000.

5. (previously amended) A process as claimed in claim 1, wherein the mixture is

granulated by heating to from 45 to 100°C.

6. (previously amended) A process as claimed in claim 1, wherein the particle size of the active ingredients employed is in a range from 20 to 700 μm.

7. (previously amended) A process as claimed in claim 1, wherein the excipients employed are fillers, disintegrants and adsorbents, lubricants, flowability agents, dyes, stabilizers, antioxidants, wetting agents, preservatives, release agents, flavorings or sweeteners.

8. (previously amended) A process as claimed in claim 1, wherein fillers are selected from the group consisting of lactose, cellulose powder, mannitol, calcium diphosphate and starch are employed as excipients.

9. (previously amended) A process as claimed in claim 1, wherein the granules can be produced by employing the process of mixer granulation, fluidized bed granulation or extrusion granulation.

10. (currently amended) A process as claimed in claim 1, wherein production is possible either continuously or batchwise.

11. (currently amended) A process as claimed in claim 1, wherein further processing of the granules, principally the forced screening, can take place either in the hot state or in the cooled state.

12. (previously amended) A process as claimed in claim 1, wherein besides the formulated mixture of polyvinyl acetate and polyvinylpyrrolidone, further release-sustaining excipients may optionally be employed before, during or after the

granulation.

13. (previously amended) A process as claimed in claim 1, wherein water-soluble, water-soluble highly swelling or lipophilic excipients are employed for further modification of release.

14. (previously amended) A process as claimed in claim 1, wherein the water-soluble polymers employed are alginates, pectins, galactomannans, carrageenans, dextran, curdlan, pullulan, gellan, chitin, gelatin, xanthans, hemicelluloses, cellulose derivatives are selected from the group consisting of methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose and carboxymethylcellulose; starch derivatives selected from the group consisting of carboxymethylstarch, degraded starch, maltodextrins, polyacrylic acid, polymethacrylic acid, acrylic acid/methacrylic acid copolymers, polyvinyl alcohols, high molecular weight polyethylene glycols, polyoxyethylene/polyoxypropylene block copolymers and high molecular weight polyvinylpyrrolidones.

(2) 1 cont.

15. (previously amended) A process as claimed in claim 1, wherein the lipophilic substances employed are fatty alcohols consisting of stearyl alcohol; fatty acids selected from the group consisting of stearic acid, glycerides, fatty acid esters and fatty alcohol esters; lipophilic polymers selected from the group consisting of ethylcellulose, cellulose acetate, acrylic ester/methacrylic ester copolymers, methacrylic acid/acrylic ester copolymers, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropylmethylcellulose acetate phthalate, and

hydroxypropylmethylcellulose acetate succinate.

16. (previously amended) A process as claimed in claim 1, wherein the water-soluble polymers are selected from the group consisting of: polyvinyl alcohols, polyethylene glycols, polyoxyethylene/polyoxypropylene block copolymers, polyvinylpyrrolidones, vinyl acetate/vinyl pyrrolidone copolymers, polyethylene glycols, polyvinylpyrrolidones, vinyl acetate/vinylpyrrolidone copolymers or maltodextrins, and salts thereof.

17. (currently amended) An oral dosage form comprising

a) a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone

b) at least one active ingredient

c) optionally water-soluble polymers or low or high molecular weight lipophilic additives

d) and, optionally, excipients,

wherein the mixture of a) to d) or a) to c) or a) and b) and d) or a) and b) is granulated by heating to from 40°C to 130°C.

C1 cont.

18. (previously amended) An oral dosage form as claimed in claim 17, which comprises as active ingredients food supplements or additives, vitamins, minerals or trace elements or active pharmaceutical ingredients.

19. (previously amended) An oral dosage form as claimed in claim 18, which comprises active pharmaceutical ingredients as active ingredients.

20. (previously amended) An oral dosage form as claimed in claim 18, wherein the

active pharmaceutical ingredient is selected from the group consisting of benzodiazepines, antihypertensives, vitamins, cytostatics, anesthetics, neuroleptics, antidepressants, antibiotics, antimycotics, fungicides, chemotherapeutics, urologicals, platelet aggregation inhibitors, sulfonamides, spasmolytics, hormones, immunoglobulins, sera, thyroid therapeutics, psychopharmaceuticals, antiparkinson agents and other antihyperkinetics, ophthalmologicals, neuropathy products, calcium metabolism regulators, muscle relaxants, lipid-lowering agents, liver therapeutics, coronary agents, cardiac agents, immunotherapeutics, regulator peptides and their inhibitors, hypnotics, sedatives gynecologicals, antigout agents, fibrinolytics, enzyme products and transport proteins, enzyme inhibitors, emetics, perfusion promoters, diuretics, diagnostics, corticoids, cholinergics, biliary therapeutics, antiasthmatics, bronchospasmolytics, beta-receptor blockers, calcium channel blockers, ACE inhibitors, arteriosclerosis remedies, antiinflammatory agents, anticoagulants, antihypotensives, antihypoglycemics, antifibrinolytics, antiepileptics, antiemetics, antidotes, antidiabetics, antiarrhythmics, antianemics, antiallergics, anthelmintics, analgesics, analeptics, aldosterone antagonists and weight-reducing agents.

C1 cont.

21. (previously amended) An oral dosage form as claimed in claim 17, which is used to produce compressed tablets.

22. (previously amended) A drug product with delayed release of active ingredient,

which is an oral dosage form as claimed in claim 17.

23. (previously amended) A drug product for delayed release of active ingredient, which is an oral dosage form as claimed in claim 17 which has been produced by compression.

C1 - cancelled

24. (currently amended) The method of delaying the release of an active ingredient comprising producing the oral dosage forms of claim 17 as drug products.

25. (currently amended) The method of delaying the release of at least one active ingredient comprising producing the oral dosage form of claim 17 wherein the at least one active ingredient comprises food supplements or additives, vitamins, minerals or trace elements.